

In the Specification:

Applicants submit a Substitute Specification at Exhibit A. A marked-up version of the Substitute Specification is provided at Exhibit B.

In the Claims:

Please cancel claims 15, 22, 31, and 38. Please add claims 50-77. Please amend claims 12, 13, 17, 19, 20, 27, 33, 35, 36, 37, 44, and 45, as follows:

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12. (Amended) A method for preparing a suppression effector and replacement nucleic acid, said method comprising:

a) preparing a suppression effector that binds to a coding region of a mature RNA encoding a mutant allele, thereby to inhibit the expression of the mutant allele; and

b) preparing a replacement nucleic acid that encodes a wild-type or non-disease causing allele and that comprises at least one degenerate / wobble nucleotide that is altered so that the replacement nucleic acid is not suppressed, or is only partially suppressed, by the suppression effector.

13. (Amended) A method for preparing a suppression effector and replacement nucleic acid, the method comprising:

a) preparing a ribozyme that cleaves a mature RNA encoding a mutant allele; and

b) preparing a replacement nucleic acid that encodes a wild-type or non-disease causing allele and that comprises at least one degenerate / wobble nucleotide that is altered so that the replacement nucleic acid is not suppressed, or is only partially suppressed, by the ribozyme.

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17. (Amended) The method of claim 12, wherein the suppression effector is an nucleic acid.

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19. (Amended) The method of claim 12, wherein the suppression effector is a ribozyme that cleaves an RNA encoded by the mutant allele.

20. (Amended) The method of claim 19, wherein the ribozyme cleaves the RNA at an NUX ribozyme cleavage site.

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27. (Amended) The method of claim 21, wherein the expression vector is a viral expression vector.

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33. (Amended) The kit of claim 44, wherein the suppression effector is an nucleic acid.

35. (Amended) The kit of claim 44, wherein the suppression effector is a ribozyme that cleaves an RNA encoded by the mutant allele.

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36. (Amended) The kit of claim 35, wherein the ribozyme cleaves the RNA at an NUX ribozyme cleavage site.

37. (Amended) The kit of claim 44, wherein the suppression effector is operatively linked to an expression vector.

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44. (Amended) A kit comprising:

a suppression effector that suppresses the expression of a mature RNA encoding a mutant allele; and

a replacement nucleic acid that encodes a wild-type or non-disease causing allele that is not suppressed, or is only partially suppressed, by the suppression effector and that differs from the mutant allele in at least one degenerate / wobble nucleotide.

G<sup>8</sup>

45. (Amended) A kit comprising:

at least one ribozyme that cleaves a mature RNA encoding a mutant allele; and

a replacement nucleic acid that encodes a wild-type or non-disease causing allele and that is not suppressed, or is only partially suppressed, by the suppression effector, wherein the replacement nucleic acid differs from the mutant allele in at least one degenerate / wobble nucleotide.

~~50.~~ (New) The method of claim 26, wherein the expression vector is a viral expression vector.

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~~51.~~ (New) A therapeutic composition, the composition comprising:

a) a suppression effector that binds to the coding region of a mature RNA encoding a mutant allele, thereby to inhibit the expression of the mutant allele; and

b) a replacement nucleic acid that encodes a wild-type or non-disease causing allele and that comprises at least one degenerate / wobble nucleotide that is altered so that the replacement nucleic acid is not suppressed, or is only partially suppressed, by the suppression effector.

~~52.~~ (New) A therapeutic composition, the composition comprising:

a) a ribozyme that cleaves a mature RNA encoding a mutant allele; and

b) a replacement nucleic acid that encodes a wild-type or non-disease causing allele and that comprises at least one degenerate / wobble nucleotide that is altered so that the replacement nucleic acid is not suppressed, or is only partially suppressed, by the ribozyme.

53. (New) The composition of claim 51, wherein the suppression effector is a nucleic acid or a peptide nucleic acid (PNA).

54. (New) The composition of claim 51, wherein the suppression effector is a nucleic acid that forms a triple helix with the mutant allele.

55. (New) The composition of claim 51, wherein the suppression effector is an nucleic acid.

56. (New) The composition of claim 51, wherein the suppression effector is a single-stranded RNA.

57. (New) The composition of claim 51, wherein the suppression effector is a ribozyme that cleaves an RNA encoded by the mutant allele.

58. (New) The composition of claim 57, wherein the ribozyme cleaves the RNA at an NUX ribozyme cleavage site.

59. (New) The composition of claim 51, wherein the suppression effector is operatively linked to an expression vector.

60. (New) The composition of claim 52, wherein the ribozyme is operatively linked to an expression vector.

61. (New) The composition of claim 59 or 60, wherein the expression vector is a viral expression vector.

62. (New) The composition of claim 51 or 52, wherein the replacement nucleic acid encodes a protein selected from the group consisting of mammalian rhodopsin, collagen 1A1, collagen 1A2 and peripherin.

63. (New) The composition of claim 51 or 52, wherein the replacement nucleic acid is operatively linked to an expression vector.

64. (New) The composition of claim 63, wherein the expression vector is a viral expression vector.

65. (New) The composition of claim 52, wherein the ribozyme comprises a sequence selected from the group consisting of nucleotides 101 - 137 of SEQ ID NO:4, nucleotides 116 - 153 of SEQ ID NO:14, nucleotides 112 - 148 of SEQ ID NO:15, and nucleotides 107 - 141 of SEQ ID NO:18.

66. (New) The method of claim 13, wherein the ribozyme comprises a sequence selected from the group consisting of nucleotides 101 - 137 of SEQ ID NO:4, nucleotides 116 - 153 of SEQ ID NO:14, nucleotides 112 - 148 of SEQ ID NO:15, and nucleotides 107 - 141 of SEQ ID NO:18.

67. (New) The kit of claim 45, wherein the ribozyme comprises a sequence selected from the group consisting of nucleotides 101 - 137 of SEQ ID NO:4, nucleotides 116 - 153 of SEQ ID NO:14, nucleotides 112 - 148 of SEQ ID NO:15, and nucleotides 107 - 141 of SEQ ID NO:18.

68. (New) The kit of claim 45, wherein the ribozyme is operatively linked to an expression vector.

69. (New) The kit of claim 37 or 68, wherein the expression vector is a viral expression vector.

70. (New) The method of claim 12 or 13, wherein the suppression effector suppresses both alleles of an endogenous gene.

71. (New) The kit of claim 44, wherein the suppression effector suppresses both alleles of an endogenous gene.

72. (New) The kit of claim 45, wherein the ribozyme suppresses both alleles of an endogenous gene.
73. (New) The composition of claim 51, wherein the suppression effector suppresses both alleles of an endogenous gene.
74. (New) The composition of claim 52, wherein the ribozyme suppresses both alleles of an endogenous gene.
75. (New) The method of claim 12 or 13, wherein the RNA is an mRNA.
76. (New) The kit of claim 44 or 45, wherein the RNA is an mRNA.
77. (New) The composition of claim 51 or 52, wherein the RNA is an mRNA.--

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**REMARKS**

Upon entry of the amendment, claims 12-22, 25-27, 30-38, and 41-77 are pending. Claims 15, 22, 31, and 38 have been cancelled. Claims 12, 13, 17, 19, 20, 27, 33, 35, 36, 44, and 45 have been amended. Claims 50-77 have been added. Applicants respectfully submit that no new matter is introduced by the present Amendment. Support for the claim amendment is found, for example, on page 7, lines 6-9 and page 10, lines 26-29 of the substitute specification. Support for new claims 50-70 is found, for example, in the claims as pending. Support for new claims 71-74 is found, for example, on page 11, lines 19-23. Support for new claims 75-77 is found, for example, on page 10, lines 26-29. A marked-up copy of the amended claims and a clean copy of the pending claims is attached herewith for the Examiner's convenience.

**Claim Objections**

The Examiner objected to claim 27 under 37 CFR §1.75(c) as being in improper form for depending from another multiple dependent claim. Accordingly, Applicants have amended claim 27 to depend only from claim 21 and have introduced claim 50, which depends only from claim 26, thereby removing the multiple dependency of the claim.